REMARKS/ARGUMENTS

In response to the Rejection mailed August 17, 2004, Applicants have amended claims 1, 3, 6, 23 and 40, added new claim 54 and present the following remarks. Claims 1-4, 6-23, 29, 37-40 and 54 are pending. Claims 5, 24-28, 30-36 and 41-53 have been canceled.

The specification was objected to as not indicating the parent provisional patent application on line 1 of the specification. The specification has been amended accordingly.

Claim 40 was objected to as missing a hyphen or word in the range of dosages. Claim 40 has been amended to correct the typographical error.

Claims 1-10 and 17-23 were rejected under 35 USC 101 as being non-statutory subject matter. The examiner contends that the claimed polypeptide self-antigen reads on the corresponding naturally occurring polypeptide. This rejection is respectfully traversed.

The claimed composition of matter is different from naturally occurring compositions by at least feature (b) and (d) as recited in claim 1 as amended. The similar naturally occurring composition is not "produced in a cell or organism that has been transformed or transfected with a nucleic acid encoding a peptide sequence. Likewise for claims 2 and 3. Secondly, the naturally occurring compositions are not "capable of inducing an immune response in a mammal, including said subject". If the naturally occurring composition induced an immune response, the subject would essentially cure itself before a B-cell lymphoma was apparent in the subject. Claims 17 recite a polypeptide in solution. The B-cell lymphoma surface immunoglobulin is not in solution but rather on the surface as its name indicates. Claim 18 recites the polypeptide in a delivery system. Such a delivery system is not connected to the natural state of the polypeptide. Accordingly, the rejection should be withdrawn.

Claims 1-23, 29 and 37-40 were rejected under 35 USC 112, second paragraph as indefinite in several recitations.

The term "derived" was considered indefinite apparently because it can be confused with chemically modified. Claim 1 has been amended to substitute different language for comparable meaning.

Claim 1 was considered indefinite by reciting "encoded at least in part". As presently amended, this claim is not indefinite as the minimal "part" is defined by feature (a) of claim 1.

Claim 1 was considered indefinite by reciting "at risk of developing a tumor". Claim has been amended to clarify that the tumor is the B-cell lymphoma. One example of this peptide being used as a vaccine in humans was with patients who had been treated for a B-cell lymphoma and were presently in remission. Unfortunately this type of tumor frequently reoccurs in the many patients, making them probably the most at risk population. It is unclear whether it is proper to designate such patients as continually having the B-cell lymphoma or that, perhaps temporarily; they no longer have the B-cell lymphoma. Regardless, such individuals are "at risk of developing a tumor. Other situations may make a person at risk of developing a B-cell lymphoma but as the vaccine involves a patient specific epitope, this language is not intended to encompass the general population.

Claim 20 was considered to lack antecedent basis for "said subject". This rejection is traversed. "Said subject" refers to a subject in claim 1, from which the nucleic acid sequence information was derived and used to prepare a nucleic acid for transfection or transformation into a cell in order to prepare the polypeptide of the present invention. The "mammalian host" is the recipient of the vaccine. The recipient may be either the same individual as "said subject" or it may be another animal, such as a test animal to test the vaccine before it is administered to a patient.

Claim 23 was considered indefinite in the recitation "at least about". This rejection is traversed. The term "at least about" is a conventional U.S. Patent claim language to designate a range with no upper limit and where the lower limit is about a given value. Examples of patents issued within the last year including this claim language include: 6,808,721 designating range of ingredient amounts in a pharmaceutical, 6,818,782, 6,818,739, 6,818,639, and 6,818,810 designating a range in

chemical, biotechnology and pharmaceutical compositions. According, there is nothing indefinite in the use of this term.

Claim 23 was considered to lack antecedent basis for "said polypeptide antigen". The claim has been amended to avoid this language.

Claims 1-23, 29 and 37-40 were rejected under 35 USC 112, first paragraph, for lack of enablement. The examiner specifically notes that the specification fails to support using any self-antigen for the treatment of a tumor and also fails to support using a B-cell lymphoma immunoglobulins antigen for any tumor. The contention is that undue experimentation is needed to use a B-cell lymphoma vaccine for different types of tumors and that other types of tumor vaccines would be useful against B-cell lymphoma. This rejection is respectfully traversed.

While not agreeing with the reasons for the rejection, applicants have amended the claims without prejudice to recite that the polypeptide self-antigen contains an epitope from a B-cell lymphoma. Also, the claims now indicate that the polypeptide may be used as a vaccine for B-cell lymphoma patients. Accordingly, this rejection is moot and should be withdrawn.

Applicants take exception to the statement that "Thus, applicants is not enabled for any vaccine composition." While the scientific literature shows many failed attempts at cancer vaccines, several different compositions have showed some positive results. While far from completely effective in all patients, considerable data has shown some improvement with some compositions. For example, effective treatment of melanoma with over 30% remission rates (data from a competitor of the assignee) may not be perfect but it does represent a success. Various types of antigens from B-cell non-Hodgkin's lymphoma have been used with some success (when the patient was not too close to death) as shown in the references of record. The rejection even relies on some of the successful results to use in rejections under 35 USC 102(b). Furthermore, on June 2. 2003, applicants provided data from the Phase I clinical trials of 16 patients with B-cell lymphomas and the positive results there from. Therefore, applicants have enabled producing a composition and shown that it is likely to work and subsequently proven that 0the claimed composition is effective as a vaccine.

The present claims have been narrowed substantially without prejudice to expedite prosecution of this application only as the example of treating B-cell lymphoma patients with a B-cell lymphoma specific epitope vaccine is perhaps best exemplified. As such this rejection is moot and should be withdrawn.

Claims 1-11, 17-23, 29 and 37-40 were rejected under 35 USC 112, first paragraph as enabling only B-cell lymphoma surface immunoglobulin antigens having the full complement of both VH and VL domains of 3 CDRs each. To support the examiner's speculation as to what is needed, he refers to Benvenuti et al to urge that the "highly specific anti-idiotypic immune response that strictly depends on the quanternary structure of the idiotype". Applicants agree that the three-dimensional structure of the polypeptide antigen is probably important. However, the full set of CDRs may not be the critical feature.

Applicants had noted that many idiotypic polypeptide vaccines do not induce a good immune response without customizing the linker. As shown in the specification examples, applicants have noted that when the linker is changed the VL and VH are arranged differently and induce a different immune response with many linkers rendering the molecule completely useless as a vaccine. Applicants solved this problem by generating many polypeptides each with different linkers, the subject of which is mentioned in claims 13-16. Each of the many polypeptides was screened to select the best one.

Benvenuti et al does not even look at the issue of the importance of the linker. They are looking at one small piece of the puzzle from one experiment. Of course it would be preferred to have as much of the surface immunoglobulins as possible to most closely resemble the natural tumor antigen on theoretical grounds alone. However, in both Benvenuti et al and the present invention, we are dealing with scFv mimicking only part of the natural tumor antigen.

While Benvenuti et al suggests that a different immune response is generated from scFv with both VH and VL as compared to only one, this does not indicate how many CDRs and of what type are needed. Also, because each patient's B-cell lymphoma surface immunoglobulins idiotype is different, it is mere speculation to state exactly which CDRs on which chains are essential.

By contrast, the present claims recite that the polypeptide self-antigen is "in correctly folded form, without a need for denaturation and renaturation and mimics said surface immunoglobulin epitope or epitopes in their native form". Benvenuti et al is immunizing the recipient with a naked DNA whereas applicants are immunizing the recipient with a polypeptide self-antigen. It is not clear whether their polypeptide (assuming one is even made in vivo) is correctly folded or not, we only know the immune response to it and therefore, Benvenuti et al does not state what is needed for a protein-based antigen at all.

Also, the present claims recite that the polypeptide self-antigen "is capable of inducing an immune response in a mammal, including said subject, without a need for adjuvant or other immunostimulatory materials". Therefore, the present claims only enabled polypeptide self-antigens, regardless of which combination of linkers, chains and CDRs needed. Accordingly, the rejection should be withdrawn.

Claims 1-13, 17-22, 29 and 38 were rejected under 35 USC 102(b) as being anticipated by Casper et al. The examiner contends that the fusion protein vaccine taught is the same as that claimed. This rejection is respectfully traversed.

The polypeptide produced by Casper et al is a fusion protein of the scFv and GM-CSF. Because another protein is fused to it, there is no assurance that the polypeptide is correctly folded or that the specific antigenic epitope is maintained. Indeed, the data shown in Figure 2 indicates that the peptide is an inferior immunogen to the natural antigen conjugated to KLH. The same figure suggests that the DNA encoding the scFv is even superior to the scFv protein fused to GM-CSF. This suggests that the GM-CSF protein portion fused to the scFv is detrimental, the most likely reason being interfering with protein folding or blocking of the epitope. Either way, this suggests that the polypeptide self-antigen in Casper et al is not "in correctly folded form" as recited in claim 1 feature (c).

Furthermore, claim 1 feature (d) indicates the polypeptide "is capable of inducing an immune response in a mammal, including said subject, without a need for adjuvant or other immunostimulatory materials." The polypeptide in Casper et al contains GM-CSF, a well-known material for enhancing the immune response. The other polypeptide in Casper et al is conjugated to KLH, a well-known adjuvant. Neither composition, meets

the requirements of claim 1 feature (d). As noted above, the scFv containing composition had inferior antigenicity and therefore one would not be motivated to remove GM-CSF for fear of a further lessening of the immune response. Accordingly, Casper et al does not anticipate the presently claimed invention.

Claims 2-4 provide for production of the polypeptide in plant cells. Plant cells have a different physiology from animal cells and therefore one may not assume that they will fold and process the polypeptide in the same manner as naturally occurs in human cells. Therefore, these claims are also not suggested by Caspar et al.

Claims 1-12, 17-23, 29 and 38 were rejected under 35 USC 102(b) as being anticipated by Hawkins et al. The examiner contends that Hawkins teaches an scFv mimicing the surface immunoglobulins of a B-cell lymphoma used as a vaccine. This rejection is respectfully traversed.

As stated above for the rejection over Caspar et al, there is no indication that the polypeptide is folded correctly or that is it capable of inducing an immune response without an adjuvant or immunostimulatory agent. The approach of using DNA vaccines lacks any suggestion of a correctly folded protein being produced because the scFv nucleic acid construct is artificial. Accordingly, the rejection should be withdrawn.

Again, claims 2-4 provide for production of the claimed polypeptide in plant cells. Plant cells have a different physiology from animal cells and therefore one may not assume that they will fold and process the polypeptide in the same manner as naturally occurs in human cells. Therefore, these claims are also not suggested by Hawkins et al.

Claims 1-23, 29 and 37-40 were rejected under 35 USC 103 as being unpatentable over Caspar et al in view of Fiedler et al, Tang et al and Hakim et al. Caspar et al was applied above. Fiedler et al is cited to disclose producing high quantities of scFv in transgenic plants. Tang et al is cited to disclose selecting scFvs from genes with randomized linker DNA sequences. Hakim et al is cited to disclose conjugating a strong antigenic carrier to or fusing another gene with a scFv. From these, the examiner concludes it obvious to optimize the scFv linker and to use an adjuvant or lymphokine to enhance immunogenicity and to prepare the scFv in plant cells. This rejection is respectfully traversed.

All of the comments above regarding the deficiencies of Caspar et al apply here as well. None of the secondary references compensate for the basic deficiencies of not teaching a correctly folded polypeptide or a polypeptide that will elicit an immune response without an adjuvant or immunostimulatory material.

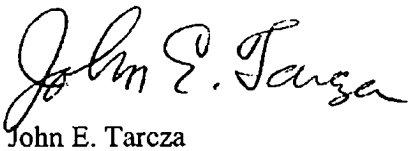
The fact that scFvs can be produced in plant cells and that these bind to antigens does not establish that they can induce an immune response in a mammalian host, much less an immune response to treat a B-cell lymphoma. Even if one accepted Tang et al as teaching linker randomization for the present polypeptide, the randomization process used in Tang et al is performed differently and would produce a different result from the present invention's linker optimization. Tang et al's linker is 18 amino acids long, being encoded by $(SNN)_{18}$ as stated in the sentence bridging pages 15682 sand 15683. The Tang et al linker is a series of truly random nucleotides. Claims 14-16 provide for "a repeated pattern of degenerate repeated triplet nucleotides" with specific nucleotides at certain locations. This is a controlled set, not a truly random chain. Thus no combination of references suggests these features. While Hakim et al teaches various proteins and peptides fused to scFvs to increase their immunogenicity, these are fused proteins. The present invention adds immunostimulatory agents separately to the vaccine composition. This two separate protein composition is not taught. Therefore, even if combined, the present invention is not taught and therefore the rejection should be withdrawn.

Claims 1-23, 29 and 37-40 were provisionally rejected under 35 USC 101 as claiming the same invention as the same claims in co-pending application 10/067,790. The present claims have been amended and therefore the claims are not the same rendering this rejection moot. Should the examiner consider a rejection under obviousness-type double patenting, applicants request such an issue be resolved once the claims are in condition for allowance in either 10/067,790 or the present application.

In view of the above amendments and comments, the claims are now in condition for allowance and applicants request a timely Notice of Allowance be issued in this application. If needed, applicants petition for sufficient extension of time for consideration of this paper.

The commissioner hereby is authorized to charge payment of any fees, including extension of time fees, under 37 CFR § 1.17, which may become due in connection with the instant application or credit any overpayment to Deposit Account No.500933.

Respectfully submitted,



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